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(19)(CA) # CANADIAN PATENT

(54) PROCESS FOR THE PRODUCTION OF PYRAZOLO [3,4-b] PYRIDINES

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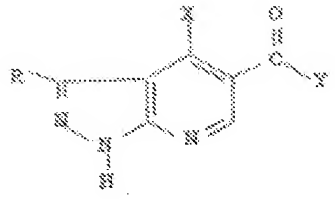
This invention relates to a new process for the production of compounds having the pyrazolo[3,4-b]pyridine nucleus and characterised by being unsubstituted in the 1-position, i.e. there is only a free hydrogen and no other substitution on the nitrogen in that position, having any of a variety of substituents in the 4-position and a carbonyl group attached to the 5-position. The 3-position may be unsubstituted or substituted. The 6-position is preferably, but not necessarily, unsubstituted. The substituent in the 4-position may be hydroxy, halo, lower alkoxy, an acyclic or heterocyclic amino radical of the type described below or a hydrazino group. In the 5-position, the carbonyl group attached to the ring carbon may bear a hydroxy, lower alkoxy, phenyl or substituted phenyl group or an acyclic or heterocyclic amino radical of the type previously referred to.

A more particular group of compounds to which the process of this invention relates are pyrazolo[3,4-b]pyridines, which are unsubstituted in the 1-position, having the general formula

(I)



R is hydrogen, phenyl or lower alkyl: X is hydroxy, halo, (preferably chloro), lower alkoxy or an acyclic or heterocyclic amino radical $-N\begin{matrix}R_1\\R_2\end{matrix}$ wherein R_1 and R_2 each is hydrogen,

lower alkyl, lower alkenyl, lower alkanoyl, phenyl, substituted phenyl (i.e. the phenyl ring contains one or two simple substituents, including lower alkyl, halogen, trifluoromethyl, amino or carboxy, preferably one of the latter three substituents) phenyl-lower alkyl, di-lower alkylamino-lower alkyl, benzoyl, substituted benzoyl, (wherein the phenyl has the same substituents referred to above) or phenyl-lower alkanoyl. Y is hydroxy, lower alkoxy, phenyl or substituted phenyl (the phenyl substituents being the same or referred to above).

A compound wherein X is a hydrazino group $-NH-N\begin{matrix}\nearrow R_3\\ \searrow R_4\end{matrix}$, wherein R_3 and R_4 each is hydrogen, lower alkyl or phenyl, may be obtained from the foregoing wherein X is alkoxy or chloro. Hydrazones may be obtained from the hydrazine, wherein R_3 and R_4 are hydrogen by reaction with an aldehyde or ketone. A compound wherein Y is an amino radical $-N\begin{matrix}\nearrow R_5\\ \searrow R_6\end{matrix}$, wherein R_5 and R_6 have the same meaning as R_1 and R_2, may be obtained from the foregoing wherein Y is alkoxy or chlorine.

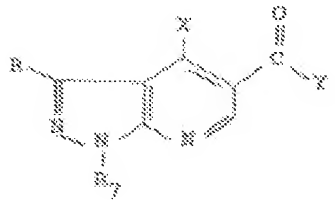
The lower alkyl groups in any of the foregoing radicals are straight or branched chain hydrocarbon groups of up to seven carbon atoms like methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. The lower alkenyl are similar groups with one double bond. References to lower alkoxy are to ether groups bearing alkyl groups of the foregoing type.

All four halogens are contemplated but chlorine and bromine are preferred, especially the first.

The lower alkanoyl groups are the acyl groups of the lower fatty acids.

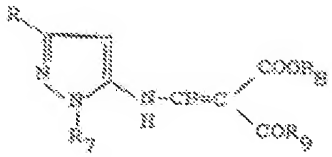
Pyrazolo[3,4-b]pyridines of the kind described above and in particular pyrazolo[3,4-b]pyridines which correspond to formula I, but bear a substituent on the nitrogen in the 1-position, e.g. those having the formula

(II)



may be produced directly by cyclising, or from compounds formed by cyclising, 1-substituted-{[(5-pyrazolyl)amino]methylene} carboxylic acid esters, e.g. compounds of the formula

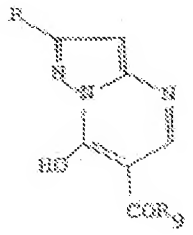
(III)



R has the same meaning as defined above, R_7 is lower alkyl, phenyl or phenyl-lower alkyl, R_8 is lower alkyl and R_9 is lower alkoxy, phenyl or substituted phenyl.

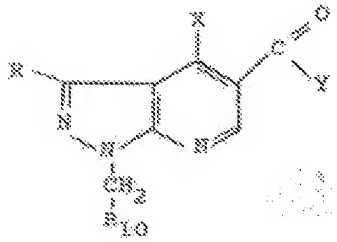
This procedure is not successful for the production of 1-unsubstituted pyrazolo[3,4-b]pyridines because (pyrazolylamino)-methylene carboxylic acid esters such as those in formula III in which there is a hydrogen atom on the nitrogen instead of the R_7 group yield on cyclization pyrazolo-pyrimidines of the type

(IV)



In order to produce 1-unsubstituted pyrazolo[3,4-b]pyridines bearing substituents in the 4- and 5-positions and particularly those compounds of formula I, it has now been found to be necessary to utilize a 1-arylmethylpyrazolo[3,4-b]pyridine or 1-heteromethylpyrazolo[3,4-b]pyridine, e.g. a compound of the formula

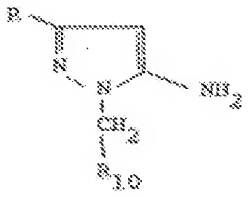
(V)



wherein R, X and Y have the same meaning as described above. R_{10} is a monocyclic or bicyclic carbocyclic aromatic or a 5- to 6-membered (exclusive of hydrogen) nitrogen, oxygen or sulfur containing heterocyclic nucleus like phenyl, naphthyl, furyl (which is preferred), thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl or the like. Cyclization in this manner yields the nucleus with the desired ring system and this, coupled with the later described oxidation step to remove the $-CH_2-R_{10}$ group, provides the desired pyrazolo[3,4-b]pyridine configuration with no substituent in the 1-positions. Variations in the group X and Y may be effected at certain stages as described below.

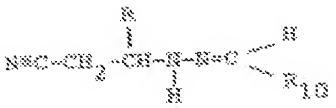
The compounds of formula V having the arylmethyl or heteromethyl group in the 1-position, which are oxidized according to this invention to obtain the 1-unsubstituted pyrazolo[3,4-b]pyridines, are derived from a 5-aminopyrazole of the formula

(VI)



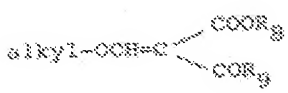
...rein R and R_{10} have the same meaning as above, which is produced by the method described in British Patent 1,057,740, published on February 8th, 1967, by ring closure of an aldehyde hydrazone of the formula

(VII)



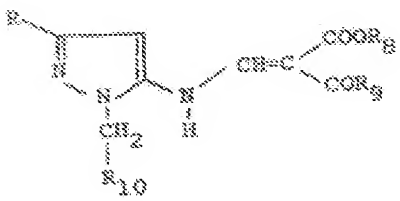
This cyclization is effected by heating at a temperature of about 90° to 130°C. in an inert liquid organic solvent, e.g., an alcohol like methanol, ethanol, butanol or the like, preferably in the presence of a catalyst such as alkali metal alcoholates like sodium butylate. This 5-aminopyrazole is reacted with an alkoxymethylene carbonic acid ester of the formula

(VIII)



This may be effected by heating the reactants at a temperature of the order of 120°C. for several hours and results in a compound of the formula

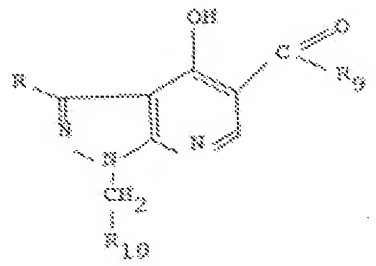
(IX)



The alkoxymethylene carbonic acid esters of formula VIII are known compounds and are produced like ethoxymethylene malonic acid diethyl ester [Organic Syntheses 28, 60-2 (1948)].

Cyclization of the compound of formula IX produces a compound of the formula

(X)

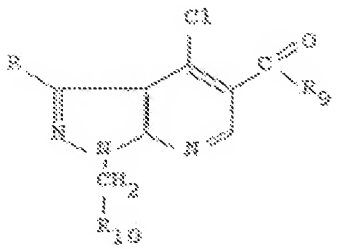


This cyclization reaction is carried out by heating the compound of formula IX in an inert organic solvent such as diphenyl ether, or the like, at a temperature of about 230 to 260°C. for several hours while removing, e.g., by distillation, the alcohol formed. The product is then separated from the solvent, e.g., by fractional distillation.

By an alternative route the cyclization of the compound of formula IX may also be effected by heating in polyphosphoric acid at a temperature of about 150° for 5 hours. The product is then separated by dilution with water.

In another method for the cyclization of compounds of formula IX, the product is refluxed with phosphorus oxychloride for 15 hours. Excess phosphorus oxychloride is removed by distillation and the compound is separated by treating of the residue with ice water. According to this method the product obtained has the formula

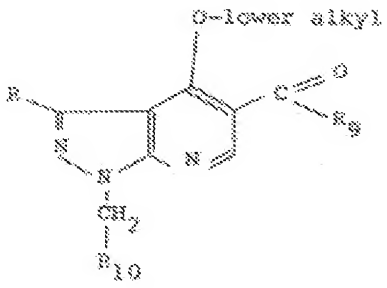
(XI)



Instead of cyclizing a compound of formula IX with phosphorus oxychloride, a compound of formula XI may be produced alternatively by chlorinating a product of formula X with an inorganic acid chloride like thionyl chloride or phosphorus oxychloride.

Reaction of a compound of formula X with an appropriate lower alkyl halide in the presence of an inorganic metal carbonate like potassium carbonate produces a compound wherein X is lower alkoxy, e.g., a compound of the formula

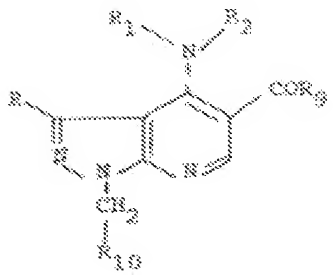
(XII)



Instead of alkylating, a compound of formula XII may also be synthesized by reacting a product of formula XI with a corresponding sodium or potassium alcoholate.

A compound wherein X is the amino radical $-N\begin{matrix}R_1\\R_2\end{matrix}$, e.g. a compound of the formula

(XIII)



may now be produced by reacting a compound of formula XII or of formula XI with a primary or secondary amine $HN\begin{matrix}R_1\\R_2\end{matrix}$.

The pyrazolo[3,4-b]pyridine unsubstituted in the 1-position is now produced according to this invention, by oxidising a compound of either formula X, XI, XII or XIII with an inorganic metal oxide oxidising agent in an inert organic solvent at a temperature within the range of about 110 to 160°C. The group on the nitrogen in the 1-position is removed and a compound having the same formula but with a hydrogen on the nitrogen in the 1-position is produced. The inorganic metal oxide oxidising agents include oxides of metals such as selenium or chromium in their highest valence states, e.g. selenium dioxide, potassium permanganate, potassium dichromate, chromic anhydride or the like; selenium dioxide is preferred. Organic solvents for the oxidation reaction include for example, diethyleneglycol-dimethyl ether, acetic acid or the like.

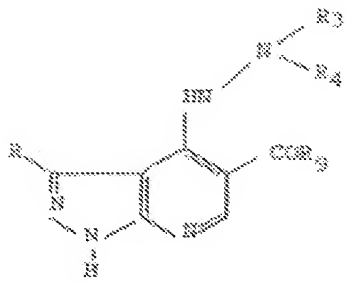
Alternatively, a compound wherein X is chloro, lower alkoxy or $-N\begin{matrix}R_1\\R_2\end{matrix}$, i.e. a compound corresponding to formulae XI, XII and XIII but having a hydrogen in the 1-position instead of the $-CH_2-R_{10}$ group, may be derived by removing the $-CH_2-R_{10}$ group from a compound of formula X by the oxidation reaction described above. This compound corresponding to formula X, but now unsubstituted in the 1-position, is treated with an inorganic acid chloride, like phosphorus oxychloride or thionylchloride as described above to produce a 1-unsubstituted 4-chloro compound corresponding to formula XI. This compound of formula XI may now alkylated with an alkali metal alcoholate as described above to yield a 1-unsubstituted-4-lower alkoxy compound corresponding to formula XII.

Treatment of the 1-unsubstituted compound of formula XII with a primary or secondary amine $HN\begin{matrix}R_1\\R_2\end{matrix}$, as previously described, produces a 1-unsubstituted-4-amino compound corresponding to formula XIII.

A compound in which Y is hydroxy is produced by saponification of the corresponding ester with an alkali metal hydroxide, such as sodium hydroxide.

When a 1-unsubstituted pyrazolo[3,4-b]pyridine with a 4-halo or 4-lower alkoxy group, e.g. a compound corresponding to either formula XI or formula XII, but without the $-CH_2-R_{10}$ group, has been obtained then a hydrazine corresponding to the formula

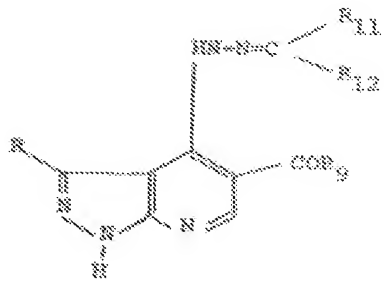
(XIV)



may be prepared by reaction of a 1-unsubstituted compound corresponding to formula XI or formula XII with the appropriate hydrazine in a solvent like alcohol. Sometimes it is advantageous to make use of an autoclave.

By reaction of a compound of formula XIV, wherein R_3 and R_4 are both hydrogen with the appropriate aldehyde or ketone, $\begin{matrix} R_{11} \\ R_{12} \end{matrix}$>C=O, a compound of the formula

(XV)



is produced. R_{11} represents hydrogen, lower alkyl, hydroxy-lower alkyl, phenyl, substituted phenyl, phenyl-lower alkyl or substituted phenyl-lower alkyl; R_{12} represents lower -alkyl, phenyl, hydroxy-lower alkyl, substituted phenyl, phenyl-lower alkyl or substituted phenyl-lower alkyl and together R_{11} and R_{12} are cycloalkyl. The substituted phenyl groups are the same as referred to previously.

A compound of formula I, in which Y is an amino group $-N\begin{matrix}R5\\R6\end{matrix}$ is formed by reaction of the corresponding carboxylic acid, i.e. Y is hydroxy, with an inorganic acid chloride, followed by treatment with the appropriate primary or secondary amine.

The various end products derived by means of this invention are useful topically as antimicrobial agents, e.g. to combat infections due to microorganisms such as Staphylococcus aureus, and also as central nervous system depressants for the relief of anxiety and tension states as more particularly described in the parent application referred to above.

The following examples are illustrative of the invention and include preferred embodiments. Other products may be obtained in the same manner by suitable alteration of the ingredients. All temperatures are on the centigrade scale.

Example 1

4-Butylamino-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

(a) [[[1-(2-Furyl)methyl-3-methyl-5-pyrazolyl]amino]methylene] malonic acid diethyl ester

177 g. of 1-(2-furyl)methyl-3-methyl-5-aminopyrazole (1 mol.) and 216 g. of ethoxymethylene malonic acid diethyl ester (1 mol.) are heated to 130° until the theoretical amount of alcohol is distilled off. The remaining oil, [[[1-(2-furyl) methyl-3-methyl-5-pyrazolyl]amino]methylene]malonic acid diethyl ester, is recrystallised from methanol, yield 305 g. (88%), m.p. 95°.

(b) 4-Hydroxy-1-(2-furyl-)methyl-3-methylpyrazolo[3,4-b] pyridine-5-carboxylic acid ethyl ester

347 g. of [[[1-(2-furyl)methyl-3-methyl-5-pyrazolyl]amino] methylene] malonic acid diethyl ester (1 mol.) are dissolved in 1 liter of diphenyl ether and heated to 240° for 2 hours. The ethanol formed is continuously distilled off. The solvent is removed in vacuo. The 4-hydroxy-1-(2-furyl) methyl-3-methyl-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester remains and is recrystallised from methanol, yield 182 g. (60%), m.p. 82°.

(c) 4-Ethoxy-1-(2-furyl)methyl-3-methylpyrazolo[3,4-b] pyridine-5-carboxylic acid ethyl ester

150 g. of 4-hydroxy-1-(2-furyl)methyl-3-methylpyrazolo-[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.5 mol.) 140 g. of potassium carbonate and 155 g. of ethyliodide are suspended in 500 ml to dimethylformamide and heated with

stirring at 60° for 10 hours. After this time, the excess potassium carbonate and precipated potassiumiodide are filtered. The filtrate is diluted with 500 ml. of water. 4-Ethoxy-1-(2-furyl)methyl-3-methylpyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester precipitates and is recrystallized from hexane, yield 125 g. (76%), m.p. 82°.

(d) 4-Butylamino-1-(2-furyl)methyl-3-methyl-4-butylamino-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

32.8 g. of 4-Ethoxy-1-(2-furyl)methyl-3-methylpyrazolo-[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.1 mol.) are dissolved in 100 ml. of dioxane and refluxed for 5 hours with 11 g. of n-butylamine (0.15 g). After this time, the solvent is evaporated to dryness and the residue is recrystallized from hexane, yield 25.5 g. of 4-butylamino-1-(2-furyl)methyl-3-methyl-4-butylamino-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (72%), m.p. 77°.

(e) 4-Butylamino-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

17.8 g. of 4-Butylamino-1-(2-furyl)methyl-3-methyl-pyrazolo[3,4-b]pyridine carboxylic acid ethyl ester (0.05 mol.) and 11.1 g. of selenium dioxide (0.1 mol.) are suspended in 50 ml. of diethyleneglycol dimethylether and heated at 160°. A few drops of water are added and the temperature is maintained for 1.5 hours. After cooling, the mixture is filtered and diluted with 20 ml. of water. Pale yellow crystals of 4-butylamino-3-methyl-1-H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester are formed and recrystallized from ethanol, yield 10.2 g. (74%), m.p. 174-176°.

Example 2

4-Butylamino-1H-pyrazolo[3,4-b]pyridine-5-diethylaminocarboxamide

(a) [[[1-(4-Picolyl)-5-pyrazolyl]amino]methylene]malonic acid diethyl ester

174 g. of 1-(4-picolyl)-5-aminopyrazole and 216 g. of ethoxymethylene malonic acid diethyl ester are heated with stirring at 140°, until the theoretical amount of alcohol has distilled off. The reaction mixture crystallizes on cooling. Recrystallisation from ethyl acetate yields 220 g. of [[[1-(4-picolyl)-5-pyrazolyl]amino]methylene]malonic acid diethyl ester (65%), m.p. 96-97°.

(b) 4-Hydroxy-1-(4-picolyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

86 g. of [[[1-(4-picolyl)-5-pyrazolyl]amino]methylene] malonic acid diethyl ester (0.25 mol.) are heated at 240° for 15 minutes. The dark oil is cooled and 200 ml. of methanol are added. 4-Hydroxy-1-(4-picolyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester crystallizes on standing, yield 33 g. (44%), m.p. 140°.

(c) 4-Hydroxy-1H-pyrazolo[3,4-b]pyridine[5]carboxylic acid ethyl ester

3 g. of 4-hydroxy-1-(4-picolyl)-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid ethyl ester (0.01 mol.) are dissolved in 20 ml. of acetic acid. 2.2 g. of selenium dioxide (0.02 mol.) and 2-3 drops of water are added. The mixture is refluxed for 30 minutes and then filtered. 4-Hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester precipitates on cooling. Recrystallization from acetic acid

yields 1.8 g. (87%), m.p. 275°.

(d) 4-Ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

4.1 g. of 4-hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.02 mol.), 5.6 g. of potassium carbonate (0.04 mol.) and 3.5 g. of ethyl iodide (0.022 mol.) are heated in 30 ml. of dimethylformamide with stirring for 10 hours at 60°. After this time, the excess potassium carbonate is filtered off and 30 ml. of water are added. 4-Ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester precipitates and is recrystallized from methanol, yield 2 g. (42.5%), m.p. 180°.

(e) 4-Butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

2.39 g. of 4-ethoxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.01 mol.) are treated with 2.2 g. of butylamine (0.03 mol.) at 90° for 1 hour. After this period the mixture is cooled, diluted with 20 ml. of water and the white crystalline precipitate is filtered off. Recrystallization from diethyl ether yields 1.7 g. of 4-butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (72%), m.p. 181°.

(f) 4-Butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid

2.6 g. of 4-butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.01 mol.) are treated with 1.1 g. of sodium hydroxide in 30 ml. of ethanol for 20 hours at room

temperature. The solvent is removed in vacuo and the residue is dissolved in 10 ml. of water. On acidification with acetic acid, 4-butylamino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid solidifies and is filtered off. The product is purified by recrystallisation from acetic acid, yield 1.9 g. (82%), m.p. 325°.

(g) 4-Butylamino-5-diethylaminocarbonyl-1H-pyrazolo[3,4-b] pyridine

2.3 g. of 4-Butylamino-1H-pyrazolo[3,4-b]-5-carboxylic acid (0.01 mol.) is refluxed with 10 ml. of thionyl chloride for 5 hours. After this time the excess of thionyl chloride is removed in vacuo, the residue dissolved in 20 ml. of dry tetrahydroforan, and 2 g. of diethylamine are added under cooling. The mixture is allowed to stand for 24 hours, then the solvent is evaporated to dryness and to the residue 20 ml. of water are added. The crystalline 4-butylamino-5-diethylamino-carbonyl-1H-pyrazolo[3,4-b]pyridine is filtered and recrystallised from ethyl acetate yield 2.1 g. (70%), m.p. 130°.

Example 3

4-(2-Cyclohexylidene)hydrazino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

(a) 4-Chloro-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

20.7 g. of 4-Hydroxy-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.1 mol.) are refluxed for 5 hours with 100 ml. of phosphorus oxychloride. The excess phosphorus oxychloride is distilled off and the oily residue poured on ice. After neutralisation with aqueous ammonia, 4-chloro-1H-

pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester separates and is recrystallised from ethanol, yield 10.5 g. (67%), m.p. 169-171°.

(b) 4-Hydrazino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester

5.6 g. of 4-Chloro-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.025 mol.) are dissolved in 10 ml. of ethanol and refluxed for 15 minutes with 1 ml. of hydrazine hydrate. On addition of 50 ml. of water, 4-hydrazino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester separates and is recrystallised from butanol, yield 3.5 g. (64%), m.p. 250°.

(c) 4-(2-Cyclohexylidene)hydrazino-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid ethyl ester

2.21 g. of 4-Hydrazino-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid ethyl ester (0.01 mol.) are suspended in 5 ml. of acetic acid. 1 g. of cyclohexanone is added and the mixture is refluxed for 10 minutes. 10 ml. of water are added. 4-(2-cyclohexylidene)hydrazino-1H-pyrazolo[3,4-b] pyridine precipitates on cooling and is recrystallized from acetic acid, yield 2.2 g. (73%), m.p. 265° (D).

Example 4

5-Benzoyl-4-(2-aminobutyl)-1H-pyrazolo[3,4-b]pyridine

(a) [[[1-(2-Furyl)methylpyrazolyl]amino]methylene]benzoylacetic acid ethyl ester

163 g. of 1-(2-Furyl)methyl-5-aminopyrazole (1 m-l.) and 248 g. of ethoxymethylene benzoyl acetic acid ethyl ester (1 mol.)

are heated at 130° until no more alcohol distills off (approximately 1 hour). The oily residue crystallizes and yields on cooling and recrystallization from hexane 310 g. of [[[1-(2-furyl)methyl-5-pyrazolyl]amino]methylene]benzoylacetic acid ethyl ester (85%), m.p. 75-77°.

(b) 5-Benzoyl-4-hydroxy-1-(2-furyl)methylpyrazolo[3,4-b] pyridine

36.5 g. of [[[1-(2-furyl)methyl-5-pyrazolyl]amino] methylene]benzoylacetic acid ethyl ester are dissolved in 50 ml. of diphenyl ether and refluxed at 260° for 30 minutes. Distillation of the solvent yields a dark oil, which crystallizes on addition of methanol. Recrystallization yields 20 g. of 5-benzoyl-4-hydroxy-1-(2-furyl)methylpyrazolo[3,4-b]pyridine (61%), m.p. 182°.

(c) 5-Benzoyl-4-ethoxy-1-(2-furyl)methylpyrazolo[3,4-b] pyridine

3.3 g. of 5-Benzoyl-4-hydroxy-1-(2-furyl)methylpyrazolo-[3,4-b]pyridine (0.01 mol.) are dissolved in 20 ml. of dimethylformamide. 2.8 g. of Potassium carbonate and 3.1 g. of ethyliodide are added and the mixture is warmed for 12 hours at 60°. Excess potassium carbonate is filtered and water is added. 5-Benzoyl-4-ethoxy-1-(2-furyl)methylpyrazolo-[3,4-b]pyridine precipitates and is recrystallized from hexane. yield 3 g. (86%), m.p. 70°.

(d) 5-Benzoyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine

1.7 g. of 5-Benzoyl-4-ethoxy-1-(2-furyl)methylpyrazolo [3,4-b]pyridine (0.005 mol.) are dissolved in 5 ml. of

diethyleneglycol dimethylether, 1.1 g. of selenium dioxide are added and the mixture is heated with stirring at 160°. After the addition of one drop of water, the temperature is maintained for 1 hour. The mixture is filtered hot and 5-benzoyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine precipitates on cooling. Recrystallization from butanol yields 1 g. (77%), m.p. 196-197°.

(e) 5-Benzoyl-4-(2-amino-butyl)-1H-pyrazolo[3,4-b]pyridine

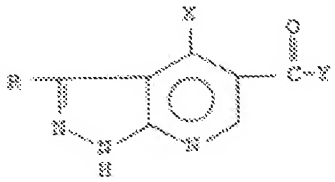
0.65 g. of 5-Benzoyl-4-ethoxy-1H-pyrazolo[3,4-b]pyridine (0.0025 mol.) are heated with 1 ml. of butylamine for 10 minutes under reflux. The mixture is cooled and 10 ml. of water are added. 5-Benzoyl-4-(2-aminobutyl)-1H-pyrazolo-[3,4-b]pyridine precipitates, is filtered and recrystallized from butanol, yield 1.1 g. (76%), m.p. 175°.

By following the foregoing example indicated in the last column, the following compounds of formula I are prepared:

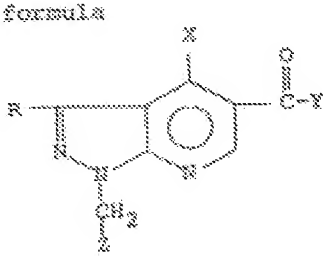
R	X	Y	m.p.	Procedure according to example
H	-OH		300°	4
H	$-NH_2$		280°	4
H	HNC_4H_9		212°	4
H_3C	$HN-C_4H_9$	-OH	245-250°	2
H	HN-	$-OC_2H_5$	224°	1
H_3C	-OH	$-OC_2H_5$	275°	2
H	HNC_4H_9	$HN-C_4H_9$	227°	2
H		$-OC_2H_5$	285°	3
H		$-OC_2H_5$	270°	3

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for preparing a compound of the formula



wherein R is hydrogen, phenyl and lower alkyl; X is hydroxy, halogen, lower alkoxy, $-NR_1R_2$ wherein R_1 and R_2 are hydrogen, lower alkyl, lower alkenyl, lower alkanoyl, phenyl which may be substituted with lower alkyl, halogen, trifluoromethyl, amino and carboxy; phenyl-lower alkyl, di-lower alkylamino-lower alkyl, benzoyl which may be substituted with lower alkyl, halogen, trifluoromethyl, amino and carboxy; and phenyl-lower alkanoyl; Y is hydroxy, lower alkoxy and phenyl which may be substituted with lower alkoxy, halogen, trifluoromethyl, amino and carboxy; comprising oxidizing with selenium dioxide a compound of the formula



wherein Z is a monocyclic carbocyclic aryl nucleus, a bicyclic carboxylic aryl nucleus and a 5- to 6-membered heterocyclic; and X, Y and R are as defined above.

2. A process as in claim 1 wherein Z is furyl.

3. A process as in claim 1 wherein Z is pyridyl.

4. A process as in claim 3 wherein R is hydrogen and Y is lower alkoxy.

5. A process as in claim 4 wherein Y is ethoxy.

6. A process as in claim 1 wherein X is lower alkoxy.

7. A process as in claim 6 wherein R is hydrogen and Z is furyl.

8. A process as in claim 6 wherein R is hydrogen, Z is furyl and Y is phenyl.

9. A process as in claim 6 wherein R is hydrogen, Z is furyl, Y is phenyl and X is ethoxy.